OUTCOMES OF ASSISTED REPRODUCTIVE TECHNOLOGIES IN WOMEN 40 YEARS AND OLDER AT TYGERBERG HOSPITAL

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Thesis submitted in fulfilment of the degree of
Master of Medicine (MMED) in Obstetrics and Gynaecology.

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DECLARATION

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December 2021

ABSTRACT

Objective: To evaluate the outcomes of ART in women age of 40 years and above

Design: Retrospective descriptive study

Setting: Tygerberg Academic Hospital, Reproductive Medicine Unit

Population: All women aged 40 years and above who had undergone ART for infertility at the Tygerberg Reproductive Medicine Unit

Methods: Medical records of all patients who qualify to be included in the study were reviewed and information regarding indications, treatment offered and outcomes were retrieved and logged in proforma data spreadsheet.

Main outcome measures:

The primary outcome measures are the LBR, OPR & CPR.

Secondary outcome measures are number of oocytes retrieved, fertilization rates, quality of embryos, cycle cancellation rates, miscarriage rates and complication rates (multiple gestations or ovarian hyperstimulation rates [OHSS]).

Results: Ovulation induction was performed on 268 women (n=268) after excluding 2 women who had used oocyte donation. The biochemical pregnancy rate was 8,2% as 22 women had a positive βhCG test on day 10. Of these, 9 had a foetal heart rate on ultrasound yielding a clinical pregnancy rate (CPR) of 3,3%. 3 pregnancies reached term with 2 being documented as having given birth and 1 lost to follow up hence the live birth rate was only 0,7% (2/268) per cycle and a miscarriage rate of 66,7%.

Conclusion: Reproductive outcomes in older women undergoing ART have a low success rate as evidenced by the low live birth rate of 0,7% and miscarriage rate of 66%. It is therefore essential that older women are thoroughly informed about expected outcomes prior to them embarking on their ART journey

Keywords: Ovarian stimulation, IVF/ICSI, ART, Older women, Mature women.

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LIST OF ABBREVIATIONS

ART	Assisted reproductive technology
PCOS	Polycystic ovary syndrome
LMIC	Low- and middle-income countries
ACOG	American College of Obstetrics and Gynaecology
IUGR	Intra-uterine growth restriction
IVF	In-vitro fertilisation
ICSI	Intracytoplasmic sperm injection
ASRM	American Society for Reproductive Medicine
CPR	Clinical pregnancy rates
SOP	Standard Operating Procedure
OCC	Oocyte-corona complexes
GV	Germinal vesicles
MI	Metaphase one
MII	Metaphase two
ICSI	Intracytoplasmic sperm injection
TVUS	Transvaginal ultrasound
GnRH	Gonadotropin-releasing hormone
DHEA	Dehydroepiandrosterone

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DEFINITIONS

- Biochemical pregnancy is defined as a pregnancy diagnosed only by detection of βhCG in serum or urine
- Clinical pregnancy is defined as a presence of a foetal heart on ultrasound at seven weeks of gestation
- Ongoing pregnancy rate is defined as the presence of a foetal heart rate on ultrasound at twelve weeks of gestation.
- Livebirth is defined as the complete expulsion or extraction from its mother of a product of fertilization, irrespective of the duration of the pregnancy, which after such separation, breathes or shows other evidence of life such as heartbeat, umbilical cord pulsation or definite movement of voluntary muscles irrespective of whether the umbilical cord has been cut or the placenta is attached.
- Infertility is the inability to conceive after 12 months of adequate (regular & unprotected) sexual exposure
- Primary infertility is when a pregnancy has never been achieved
- Secondary infertility is when at least one prior pregnancy has been achieved
- Fecundity is the probability that a cycle will result in a live birth
- Fecundability is the probability that a cycle will result in pregnancy
- Foetal viability is reached at 27 weeks of gestation and an estimated foetal weight ≥ 800 grams

CHAPTER 1: INTRODUCTION

1.1 INFERTILITY IN AN AFRICAN CONTEXT

Childbearing and rearing are important events in the life of every human being and are possibly associated with the ultimate goal of completeness, happiness and family integration [1]. In Africa motherhood is used as measure of a woman's reputation in society, a source of power, pride, an important aspect of life and cultural expectation within a marriage [2]. Hence the inability to conceive is a major problem that is stigmatising to many people and this often leads to delay in seeking treatment out of the fear of being labelled as "infertile" [3]. Women delay childbirth due to societal changes, cultural expectations and financial situations which leads to more women seeking treatment for infertility in their late reproductive years [4]. The challenges of older women seeking fertility treatment include poor outcomes, increased risk of miscarriages and pregnancy related complications. [4] Additional challenges in Sub Saharan Africa include limited access to assisted reproductive technology (ART) clinics, affordability, geographic barriers and lack of infrastructure required for ART [5].

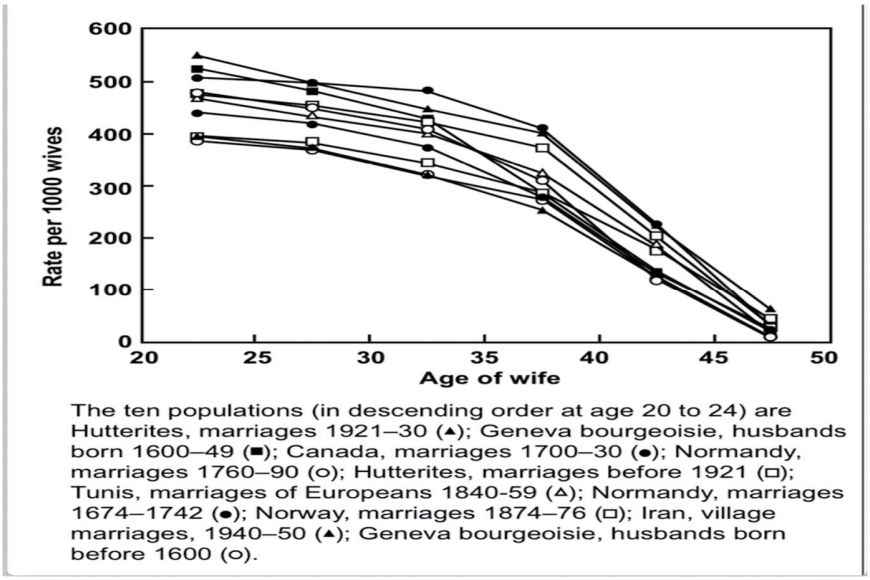
1.2 EPIDEMIOLOGY OF INFERTILITY

Infertility is defined as the inability to conceive after 12 months of regular unprotected sexual intercourse. It is estimated to affect as many as 186 million people worldwide, which is 8-12% of reproductive aged couples [6]. The population that is affected by infertility is higher in low-income countries in comparison to high-income countries. The rate of infertility is reported to be as high 30% in some regions including Sub Saharan Africa [6]. Primary infertility is more prevalent in young women of reproductive age (20-29 years) in comparison to their older counterparts (30-44 years) [2]. The prevalence of secondary infertility increases sharply with age from 2,6% in women aged 20-24 years to 27,1% in women aged 40-44 years [7]. Secondary infertility is the second most common form of female infertility around the globe with unexplained infertility being the commonest cause in women over 35 years [6,8]. Fecundity progressively declines in older women due to a decline in ovarian function in this age group, while fecundability decreases with

an increase in both maternal and paternal age [9].

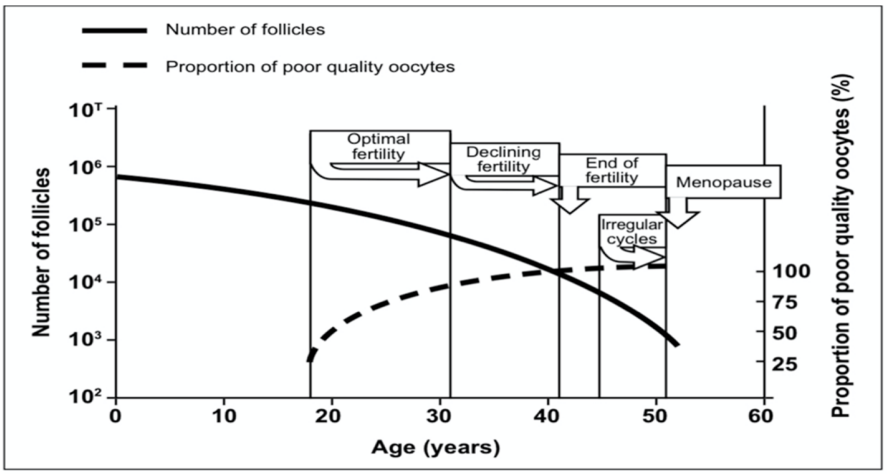
1.3 CAUSES OF INFERTILITY

The major causes of infertility include tubal and pelvic pathology (30-40%), ovulatory dysfunction (20-40%), male factors (30-40), uterine pathology is relatively uncommon, and the remainder is largely unexplained [8]. The prevalence of each cause varies with age, with ovulatory dysfunction being more common in younger than older couples and tubal and pelvic factors have a similar prevalence [8]. Male factors and unexplained infertility are observed often in older couples [8]. The most common factors associated with infertility as women age are secondary amenorrhea, polycystic ovary syndrome (PCOS), uterine myomas and endometriosis [9]. Infertility is high (25%) amongst women with PCOS and becomes more severe with age [9]. Myomas are known to increase in size and number during the fourth decade thereby reducing fertility with their effects on the endometrial cavity, altering uterine contractility and reducing endometrial receptivity [9]. The incidence of cancer during pregnancy is expected to rise with concomitant increasing age of childbearing [10]. In low and middle income countries (LMIC) genital tract infections and sexually transmitted diseases are important risk factors for tubal disease & male factor infertility [9]. Endometriosis impairs fertility via multiple mechanisms which include distortion of pelvic anatomy through the formation of adhesions, altered peritoneal function that has an adverse effect on fallopian tube function and altered hormonal and cell mediated function which may alter endometrial receptivity [11]. Nulliparity is a risk factor for endometriosis and its prevalence is highest during the third and fourth decade of life, when the modern women who has delayed childbearing often wishes to conceive [9]. Lifestyle factors such as smoking, abnormal body weight (BMI<19kg/m² and >25kg/m²), alcohol and coffee consumption, psychological and physical stress as well as environmental pollutants such as radiation have an adverse effect on fertility [9]. The probability of conception depends on oocyte quality, which is determined by the women's age; according to the American College of Obstetrics and Gynecology (ACOG) the fecundity of a women decreases gradually but significantly beginning approximately at age 32 years and decreases more rapidly after age 37 years [12].



The ten populations (in descending order at age 20 to 24) are Hutterites, marriages 1921–30 (▲); Geneva bourgeoisie, husbands born 1600–49 (■); Canada, marriages 1700–30 (●); Normandy, marriages 1760–90 (○); Hutterites, marriages before 1921 (□); Tunis, marriages of Europeans 1840-59 (△); Normandy, marriages 1674–1742 (●); Norway, marriages 1874–76 (□); Iran, village marriages, 1940–50 (▲); Geneva bourgeoisie, husbands born before 1600 (○).

Figure 1: Relationship between maternal age and natural fertility (rate of pregnancy/1000 women) as adapted from SOGG Clinical Practice Guidelines Nov 2011 [12,20].



Graph was drawn after Hansen et al. and de Bruin et al.

Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. Endocr Rev 2009;30:465–93.12 Copyright 2009, The Endocrine Society. Reproduced with permission.

Figure 2: Schematic representation of the number of primordial follicles present in the ovaries and the chromosomal quality of oocytes in relation to female age and corresponding reproductive events [20].

1.4 AGE RELATED INFERTILITY

There is a natural age-related decline in fertility that is observed even in populations that do not use contraception [12]. This is often accompanied by a decrease in oocyte quality, which can be attributed to a complex series of age-related changes in nuclear and cytoplasmic competence. These changes usually affect crucial processes such as spindle formation, mitochondrial function and cytoskeletal integrity resulting in abnormal chromosome segregation [13]. This may lead to the production of poor quality oocytes that are less likely to fertilise; and if fertilised the embryos may be slow to divide and unlikely to implant [13]. Societal factors have led to a rise in the incidence of women who delay childbearing well into their late reproductive years [14]. This in turn may lead to increased numbers of women seeking assisted reproductive technologies (ART) [15]. Women now focus on getting educated and pursuing careers which leads to an increased age at first marriage and hence delayed childbearing [14]. The driving force behind the shifting paradigm in modern reproductive forces is estimated to have begun in the 1960's with the advent and use of safe, effective, affordable and accessible oral contraceptive pills; providing women with the opportunity to control their own reproductive destinies [16]. Health education offered to adolescents tends to focus on the precautions of pregnancy prevention i.e., during contraceptive counselling, the dangers of delayed childbearing are not discussed [16]. Legalization and social acceptance of abortion in many countries has also left little room for error after failed contraception [17,18]. This decreases the chances of earlier unplanned pregnancies with childbearing being delayed until financial stability is achieved. The rise in the divorce rate has also led to a rise in second marriages at a later stage and a need to start a family with the new partners [8]. There is also a misconception that childbearing can be delayed until the later years of life with the hope that ART can compensate for age related infertility [17].

Older women are at increased risk of early pregnancy, obstetric and neonatal complications, with this risk being pronounced in women over 35 years of age [13,18]. Older women are more likely to have stillbirths, miscarriages and ectopic pregnancies [13,18].

In the general population the risk of miscarriage in women 35-39 years of age is 24% and doubles to 51% at 40-44 years of age if the women conceive on their own without the use of donor eggs [12]. A wide variety of obstetric complications are associated with advanced maternal age, these include higher chances of operative delivery, aneuploidy, caesarean section, hypertensive disorders, peri-partum cardiopathy, placenta praevia, abruptio placenta, diabetes (gestational and pregestational), multiple pregnancies, intra-uterine growth restriction (IUGR) and low birth weight [13,18]. Use of ART is associated with an increased incidence of multiple pregnancies at all ages, and this further increases the risk profile for obstetric complications [19]. Older women are more likely to have pre-existing medical disorders such as chronic hypertension and diabetes of which some may be exacerbated by pregnancy. There has been inconclusive data about the effects of infertility treatments (especially hormonal methods) on cancer development; nevertheless, older women who undergo ART should be counselled on the possible associations [10].

1.5 TREATMENT OPTIONS FOR AGE RELATED INFERTILITY

Treatment options for older women with infertility include ovulation induction & timed intercourse, ART (in-vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI) with usage of own eggs or donor eggs, adoption or childless living [20]. Proposed strategies to improve treatment outcomes in older women seeking assistance include modified ovarian stimulation protocols, assisted hatching of embryos and addition of androgens to improve oocyte quality [21]. But none of these have shown any significant improvement in the results. The most effective strategy is oocyte donation especially in women with reduced ovarian reserve [22,24]. Embryo and oocyte cryopreservation are possible options and should be considered by women who plan to delay childbearing [24]. In 2012 the American Society for Reproductive Medicine (ASRM) also declared that egg freezing should not be considered experimental and in some literature it is considered to be preventative medicine for age related fertility decline [25].

The ideal age for egg freezing is 30-35 years, from the age of 38 years there is low probability of successful thawing, fertilisation, implantation and live birth [25]. It is cost

effective to freeze oocytes at an age below 35 years. Freezing at 38 years & above is not cost effective and should not be recommended. The latter implies that there is a mismatch between patient demand and optimal outcome as the likelihood of poor outcomes is high in women aged over 40 years [25]. However, gamete donation or third party reproduction (such as surrogacy and adoption) is not always well received as it does not provide a genetic link between mother and child [23]. Third party reproduction may also pose a dilemma from a religious point of view as different religious vocations have different views; Islamic religious laws view it as adultery whereas Judaism in Israel is so receptive that it is the only country that offers government subsidy for gestational surrogacy [26]. The Catholic Church has clearly prohibited ART use, but nations influenced by Catholism have varied responses; Hinduism on the other side has not specifically addressed ART and seems to be permissible as ART accords with several characteristics of the Hindu thoughts [27]. Therefore most women will opt to attempt treatment using their own oocytes despite the risk of poor outcomes. This has led to the motivation to evaluate ART outcomes of older women (≥ 40 years) receiving treatment at Tygerberg Academic Hospital Reproductive Medicine unit, which is a low resource facility.

CHAPTER 2: RATIONALE FOR STUDY AND METHODOLOGY

2.1 RATIONALE FOR STUDY

Due to lack of guidance regarding the care of older women seeking fertility treatment in limited resource settings, this information will improve the ability of clinicians to counsel their patients regarding treatment outcomes. The study will also form the basis for future research into alternative strategies.

2.2 AIM

To evaluate ART outcomes in older women at Tygerberg Academic Hospital, Reproductive Medicine Unit.

PRIMARY OBJECTIVE

To investigate livebirth rates (LBR) and if not available, the ongoing pregnancy rates (OPR) and if not available, clinical pregnancy rates (CPR) of older women (≥ 40 years) who received ART treatment at Tygerberg Hospital.

SECONDARY OBJECTIVE

To evaluate:

- The number of oocytes retrieved
- Fertilization rates
- Embryo quality
- Cycle cancelation rates
- Miscarriage rates
- Complication rates (such as multiple pregnancies, ovarian hyper stimulation syndrome.)

2.3 METHODS

Study design: Retrospective descriptive study

Study population: All women seeking assisted reproductive technology in the form of IVF and ICSI

Setting: Tygerberg Reproductive Medicine Unit between 2016-2018

Inclusion criteria: All women 40 years and older who received ART using their own oocytes at Tygerberg Hospital

Exclusion criteria: All oocyte donation cycles were excluded as well as women younger than 40 years of age.

Data collection:

Data was obtained from patient records a using proforma data collection sheet presented as (**Appendix 3**). Data was collected using patient's folder numbers only, no names or identifiable information was used. All data was coded to protect the identity of the patients and was entered into an appropriate spread sheet for analysis

Data management & analysis:

Sample size calculation was discussed with a statistician. Data from the data collection tool was entered into a spreadsheet and analysed using the latest version of STATISTICA in consultation with a biostatistician from the Biostatistics unit. Continuous data was analysed descriptively using means and standard deviations if data is uniformly distributed, and medians and interquartile ranges if data is not uniformly distributed. The 95% confidence interval was calculated. Nominal data was presented using absolute and relative frequencies with 95% confidence interval being used for binomial proportions. For the primary outcome, an analysis of variance (ANOVA) was performed. For comparing two continuous or ordinal variables, Pearson correlations was used if data are normally distributed and the Spearman rank order correlation if data are non-normally distributed. For comparing a single binary variable with a continuous variable, a T-test was used if data are normally distributed and a Mann-Whitney U test if data are non-uniformly distributed or if heterogeneity of variance exists.

For comparing a single nominal variable with a continuous variable an appropriate ANOVA was used. If the nominal variable represents dependent groups or measurements over time the repeated measures ANOVA was performed or a Friedman's test if data is ordinal. The relation between two nominal variables was investigated with contingency tables and likelihood at chi-square tests.

Implementation of findings:

The result will be presented at relevant scientific meetings and the Academic Year Day of the Stellenbosch University. A manuscript will be prepared and submitted for publication in a national or international journal as an original research article.

Ethical consideration:

Ethics approval was obtained from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University (**Study no:1514**), prior to commencement of the study. Ethics approval is presented in (**Appendix 1**)

Informed consent:

This is a minimal risk study because it is a retrospective review of patients' medical records and application for waiver of informed consent was submitted and approved (**Appendix 2**)

Confidentiality:

All patients were assigned an individual study number that was not linked to their names or hospital numbers to protect their identities and to maintain confidentiality. Identity of the patients was only known to the principal investigator who was keeping the details of the information in a secure office and only accessed the information for verification purposes. The computer used for coding and storing patients informational is password protected.

Study timelines:

The study was envisaged to take period of approximately 6-9 months following approval from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University.

Study Limitations:

Incomplete or missing clinical information and illegible hand writings are potential limitations to the study.

Study team:

The study team comprises the Principal investigator, Supervisor, Statistician allocated from the Biostatics Unit Centre for Evidence based Health Care at the University of Stellenbosch.

Workplan:

On receipt of approval from the Health Research Ethics Committee data was collected from patients using structured questionnaires. Data was extracted, coded and entered into a spreadsheet. With the assistance of the Statistician data was analysed and interpreted. Findings were compared to available published literature and reported accordingly.

Budget:

Expected costs: stationery R1500.

The study was self-funded.

Tygerberg Reproductive Medicine Unit Protocol and Standard Operating Procedure (SOP):

- **Ovarian stimulation protocols**

  Standard ovarian stimulation protocol according to SOP of the Tygerberg Hospital Fertility Clinic were used. Ovarian stimulation occurred with the administration of medication that stimulated the ovaries to produce multiple oocytes via follicular development

- **Oocyte retrieval**

A standard oocyte retrieval procedure according to the SOP of the Tygerberg Hospital Fertility Clinic has been used. Briefly, follicular fluid was aspirated, using an ultrasound guided method and examined for the presence of oocyte-corona complexes (OCC). Subsequently the oocytes were graded germinal vesicles (GV), metaphase one (MI) and metaphase two (MII) and finally transferred to fertilization medium

- **Semen preparation**

Semen was processed using standard, routine protocols. Both the Swim up and Gradient centrifugation preparation methods were done depending on the semen characteristics

- **Fertilisation/insemination process**

Mature MII oocytes were fertilized using standard protocols of IVF and ICSI

- **Embryo culture**

Standard embryo culture methods were used. Oocytes were cultured in either sequential (fertilization, cleavage and blastocysts) or 1 Step medium (Sage®, Harrilabs) in a CO2

incubator at 37ºC for up to 5 days.

- **Embryo evaluation- specifically Day 3 embryos**

  Standard day 3 embryo evaluation for quality and morphology was followed. Embryos were graded according to the number of cells present and quality thereof using a modified Veeck *et al* classification (Veeck, 1999). Good quality embryos include the following:

Table 1: Veeck classification for embryo grading

Embryo Grading (Good Quality Criteria)		
	Cell	**Grading**
Day 2	2 3 Cell 4	4 5
Day 3	6 7 Cell 8	4 5
Day 4	10 Cell Early Compact (EC) Compact	4 5
Day 5	Blastocyst 1 B or A	1, 2, 3 B or A

All good quality embryos that were not transferred were cultured and vitrified using standard protocols

- **Follow up and pregnancy assessment**

On all patients a day 10 βhCG test was done to establish the biochemical pregnancy rate. An ultrasound was performed around 12 weeks to confirm presence or absence of a foetal heart to assess the ongoing pregnancy rate. Patients were then followed up until term or delivery.

CHAPTER 3: RESULTS

3.1 DEMOGRAPHIC DATA

There were 268 patients included in the study after excluding 3 patients who were 40 years and above but had used donor oocytes. The study population comprised of women ranging from 40-45 years of age with a mean age of 41yrs. Data was collected from the Tygerberg Reproductive Medicine Unit (treatment period 2016-2018). Unexplained infertility (39,8%) was the most common female diagnosis, followed by tubal factor infertility (30,9%) & uterine factors (16,3%) [Table 2].

Table 2: Demographic data

Demographic data	Numbers (n)	% of patients
Primary	130	48,5
Secondary	80	29,8
Unknown	58	21,6
Female diagnosis		
Idiopathic	107	39,8
Tubal factor	83	30,9
Endometriosis	34	12,6
Myoma	10	3,7
PCOS/POI	4	1,5
Male factor	7	2,6
Ovarian reserve/low AMH	6	2,2
Other	17	6,3
Male diagnosis		
Normozoospermia	94	35
Teratozoospermia	36	13,4
Testis biopsy	30	11,2
Donor sperm	25	9,3
Oligo teratozoospermia	8	2,9
Oligo astheno teratozoospermia	6	2,2
Oligozoospermia	6	2,2
Other	62	23,1

3.2 TREATMENT VARIABLES

Two different ovulation induction protocols were used on 268 patients, of which 87% received clomiphene and Menopure® (mild ovulation stimulation protocol) and 12,6% received conventional IVF stimulation protocol with GnRH antagonists [Table 3].

Table 3: Treatment variables

Stimulation protocol	**Number (n)**	**% of Patients**
Clomiphene or HMG/FSH	234	87
HMG & GnRH antagonists	34	12,6
Procedures		
ICSI	87	62,6
IVF	39	28,1
Cancelled cycles:	83	31
•Poor follicular growth	22	9,7
•No of oocytes during retrieval	26	8,2
•Poor embryo develop	34	12,7
•Unknown	1	0,4
FET	4	2,9
Cycle number		
1 cycle	136	50,7
2 cycles	61	22,7
3 cycles	27	10
4 cycles & greater	17	6,3
Unknown	27	10
Donor sperm		
No	189	72,7
Yes	71	27,3

3.3 TREATMENT OUTCOMES

Three to nine oocytes were retrieved in 52,4% of patients, with two or less being retrieved in 43,5% while a minority of patients 0,8% had more than nine oocytes. The overall cycle cancelation rate was 31%. The majority of embryos, 82,6% were transferred between day three-five, with only 1,6 % being transferred on day six and 15,7% were transferred between day one-two [Table 4].

Twenty-two women had a positive βhCG test on day ten resulting in a biochemical pregnancy rate of 8,2% (22 out of 268). The clinical pregnancy rate was 3,3% as 9 women had a positive pregnancy test as demonstrated by a positive fetal heart on ultrasound with a miscarriage rate was 66,7% as only 3 reached term. Three pregnancies reached term, however only two were recorded to have given birth with one being lost to follow up. Therefore, the live birth rate was 0,7% (2 out of 268 cycles) [Table 4].

Table 4: Treatment Outcomes

Treatment outcome	**Number (n)**	**% of Patients**
Biochemical Pregnancy rate	22	8,2
Clinical/Ongoing Pregnancy rate	9	3,3
Livebirth rates	2	0.7
Miscarriage rate	6	66
Term pregnancies	3	1,1
Number of oocytes retrieved/aspirated: 0	25	9,3
1-3	145	53,9
4-7	84	31,6
>7	6	4,9
Endometrial lining: <8mm	23	10,9
8-12mm	178	84,7
>12mm	17	2,3
Fertilisation rates	629/736 x 100	85.4
Embryo quality:		
GQE	318	82,3
PQE	68	17,6
Number of embryos transferred:		
No transfer	57	23,6
One	60	24,9
Two	58	24,1
Three	54	22,4
Four	12	5
Day of embryo transfer:		
Day 1	1	0,5
Day 2	28	15,2
Day 3	107	58,2
Day 4	19	10,3
Day 5	26	14,1
Day 6	3	1,6

CHAPTER 4: DISCUSSION

The biochemical pregnancy rate was 8,2% (22 out of 268) as measured with βhCG on day 10, with a clinical/ ongoing pregnancy rate of 3,3% (of the 22 women who had a positive βhCG on day ten, 9 had a positive foetal heart on ultrasound at seven and twelve weeks). Of the 9 pregnancies, 3 progressed to full term resulting in a miscarriage rate (MR) of 66% (6 out of 9) Table 4. In this study we confirmed 2 live births which results in a LBR of 0,7% per treatment cycle started. These findings are comparable to results reported by *Aflootian et al* 2011 in a retrospective study done in Iraq. They evaluated pregnancy outcomes of 313 women aged 40 years and above, undergoing ART. They found, biochemical pregnancy rate of 8,6%, CPR of 3,8%, MR of 63%, cancelled cycles of 23,3% and a LBR of 3,3% [28]. *Aflootian et al* define a live birth as the birth of at least one live born after 20 weeks, which in our setting would be defined as a miscarriage. Their findings and our study findings showed that the ART outcomes are generally poor in older women. However, a retrospective analysis by *Auge et al,* that involved 1939 who were 40 years and beyond using autologous oocytes reported LBR of 12,3% which is much higher than our study findings [29]. The higher LBR could be attributed to a larger sample size & a study population from a high resource setting, together with advanced neonatal facilities and therefore define foetal viability from 24 weeks gestation. The poor outcomes in terms of poor pregnancy rates, high miscarriage rates and cancellation rates reflect the poor oocyte quality in this context.

In this study we found high rates of cycle cancellation (31%) due to poor follicular growth (9,7%) no oocytes at the time of aspiration (8,2%) and poor embryo development (12,7%) among other reasons. These findings are similar to those reported by other authors [28,33,34]. The literature demonstrates that advanced maternal age seems to have an unfavourable impact on many aspects of ART such as cancellation rate, as most studies have a cancellation rate around 22-24% [28,29,33,34]. *Aflootian et al & Auge et al* found comparable cycle cancellation of 23,3% per oocyte retrieval and 22,5% respectively.

Oocyte aging which could lead to low fertilisation rates and poor quality embryos as well as oocyte depletion are known phenomenon with increasing maternal age (Figure 1 and 2). Hence these findings are typical in this age group of patients as demonstrated by the similarity of the cancellation rate despite vast differences in sample size and clinical setting. Rate of pregnancy loss is elevated in older women due to the association of aneuploidy with oocyte aging. The miscarriage rate was 66% which was comparable to that found by *Aflootian et al* of 63% but *Auge et al* had a much lower miscarriage rate of 33% [28,29]. In a retrospective analysis by *Klipstein et al* the miscarriage was significantly lower at 32,6%, a finding that pregnancy loss was lower if good quality multiple embryos were transferred and two foetal hearts were visualised [32]. To avoid raising false hope such findings should be interpreted with caution and discussed during counselling before embarking on ART with older women.

The highest number of oocytes found during aspiration in this study is 13 oocytes (0,4%). About 34,2% of patients showed poor response to ovarian stimulation (<3 oocytes), with 52,4% showing an optimal response(3-9 oocytes) & 0,8% showing an excessive response (>9 oocytes) [Table 4] with a mean of 5,5 oocytes retrieved, while *Aflootian et al* found a mean oocyte retrieval of 3,2. *Steven et al* had about 30% of patients with cancelled cycles due to poor response with mean number of oocytes retrieved of 6,8 [33]. These findings go to show that the number of oocytes is not a good predictor of ART success in older women, possibly in younger women as well. The mean number of fertilised zygotes in this study was 4,5 which is comparable by that found by Steven et al of 5,4 [33]. Supernumerary oocytes do not confer a cumulative live birth rate benefit to patients predicted to be high responders, moreover they may contribute to an increase in observed adverse effects such as ovarian hyper stimulation syndrome. Retrieval of high numbers of oocytes (>15) had a negative impact on the ongoing pregnancy rate in fresh transfer cycles with only a marginal benefit to cumulative live birth rates [41].

A retrospective cohort of 737 infertile women undergoing their initial fresh embryo non donor IVF or ICSI was done to evaluate the association between the number of mature oocytes per assisted reproductive technology cycle and the likelihood of a live birth. The study concluded that the minimum mature (phase II metaphase) oocyte yield that predicts a live birth after ART is six (6) meaning, retrieving more than six mature oocytes did not translate into a better chance for a take-home baby and conversely in cycles with five or fewer mature oocytes there was significantly lower likelihood of live birth [41]. That will mean the average 35 year old patient needs on average 5 oocytes to expect a euploid embryo while, patients over 42 years need 20 oocytes [44]. Embryo development is a good indicator of oocyte quality. In this study we found 318 (82,3%) good quality embryo and 63 (17,6%) poor quality embryo. The number of embryos transferred and the day of transfer did not seem to influence the outcomes in this study (Table 4). However, some studies suggest multiple embryo transfer and early transfer on day 2/3 is associated with better pregnancy outcomes [48]. *Combelles et al* suggested that in women > 40years, five embryos are the optimum number to transfer and transferring more than five embryos does not confer any additional benefit to clinical outcome [44]. There were no cases of multiple pregnancies and ovarian hyperstimulation reported in this study. These findings were reassuring as these complications should be minimised at all times especially in older women with co-morbidities and in resource restricted settings.

Current adjuvant treatments available have limited success in improving oocyte quality and ability to generate genetically competent embryos, making donor oocyte an option rather than solely a treatment for IVF failure [42]. Such treatments include adjuvant use of DHEA or testosterone to increase ovarian responsiveness to stimulation, human growth hormone or antioxidants like CoQ10 to potentially improve egg and embryo quality; however, results have been inconsistent without significant increases in live birth rates [42].

More favorable pregnancy and implantation rates obtained by patients could depend on the pattern of GnRH antagonist administered [38]. The latter statement was a conclusion of a study done on poor responders and women aged > 35 years randomized into group 1 (received standard long GnRH protocol) and group 2 (received recombinant human FSH and clomiphene citrate and when at least one follicle of 16mm in diameter was observed a GnRH antagonist was administered in a multi dose fashion until follicles were greater than or equal to 18mm). It was concluded that the latter protocol (group 2) could be usefully administered in poor responders and aged women to obtain lower cancellation rates, greater oocyte recovery and more favourable pregnancy and implantation rates [38].

In patients aged 40 years and over, there is a reduced ovarian reserve, with a lower number of oocytes remaining in the ovary which may lead to markedly lower expectancy of pregnancy rates per cycle in comparison to younger women [39]. A controlled randomised study was done on two hundred and twenty women who were 40 years and older undergoing IVF (ICSI) that aimed to determine the efficacy of the short versus the long GnRH analogue suppression protocols. The findings were that the long protocol performed better than the short protocol in older women as it resulted in higher numbers of oocytes harvested, higher numbers of embryos obtained, higher implantation rates and higher pregnancy rates [39]. A randomised control trial compared three different protocols of ovarian stimulation in 250 poor responder women; clomiphene citrate, high dose of gonadotrophins and antagonist (68) versus flexible GnRH antagonist (71) versus short GnRH agonist protocol (75). The study demonstrated that short GnRH agonist should be first choice in poor responders and clomiphene citrate should be avoided due to it's very low success rate. [40] For controlled ovulation induction 233 patients in the index study received clomiphene citrate and human menopausal gonadotrophin (HMG) whereas 34 received HMG and gonadotrophin releasing hormone with 1 patient receiving an aromatase inhibitor. Klipstein *et al* used one of three protocols (GnRH analogues +/- pretreatment oral contraceptives/an antagonist protocol/HMG +/- recombinant FSH) that were individualised according to patient factors with human chorionic gonadotrophin (hCG) administered in patients with 2-3 follicles greater than/equal to 14mm and the mean

number of embryo transferred was 3,1.

The outcomes were much better with a LBR that was nine times higher than that found in the index study with a lower miscarriage rate (44% vs 66%). *Klipstein & Auge et al* did not use clomiphene whereas in our study the majority of patients received a protocol containing clomiphene citrate which seems to be associated with poor outcomes in comparison to protocols containing gonadotrophin analogues.

In light of the poor pregnancy outcomes, it is advisable that couples should receive counselling regarding poor conception rates, high miscarriage rates etc. Alternative methods such as oocyte donation, surrogacy and adoption should be discussed. Oocyte donation makes up an increasingly large percentage of all ART cycles worldwide [30]. However, it presents a challenge for the clinician who not only has to serve interests of both the donor and the recipient but has to deal with a complex situation which includes synchronising both donor and recipient cycles. It is associated with stable implantation, clinical pregnancy and delivery rates among recipients aged 25 to mid- 40's [30]. Donor pregnancy rates are generally as high as 48,1% and 28,5% with use of fresh and cryopreserved oocytes respectively in the age range 40-44 years but began to decline from mid 40's to 44% and 26,65% [31]. The latter are findings of a retrospective cohort study of aggregated national cycles of donor egg therapy collected by the Society of Assisted reproductive Technology (SART) and the Centers for Disease Control and Prevention (CDC) [31]. A retrospective cohort study by *Yeh et al* showed a decline in success rates in older recipients; with an implantation rate of 40,9%, a clinical pregnancy rate of 59,9%, a live birth rate of 48,6% and a miscarriage rate of 19% in recipients who were 50 years and older [48].

For some couples oocyte donation/adoption may not be an acceptable option for various reasons including fear of not having a genetic link with the offspring, cultural, or religion. In a Japanese survey about public attitudes towards third party reproduction, 40% of responders found third party reproduction socially unacceptable because the parent child relationship will be unnatural [51].

More women are delaying childbearing due to societal changes, and advances in ART have made conception possible for women of advanced age [28]. However, advanced maternal age is associated with medical and obstetric complications and can present an ethical dilemma to clinicians. Recognizing the poor treatment outcomes based on our study findings (LBR =0,7%) and other literature reports, and taking into consideration the high costs of ART services; the question is, should we be offering ART services for women 40 years and older with autologous oocytes? This is an ethical and moral question that needs to be constructed in reproductive medicine conversations and debate. Therefore, the conversations around the age-related decline in fertility and social oocyte cryopreservation should possibly be stimulated hand in hand with reproductive health (including contraception) counselling in women of childbearing age.

4.2 STRENGTHS AND LIMITATIONS:

In our knowledge this study is the first to assess outcomes of ART in women 40 years and older in a low resource setting. This study will hopefully stimulate more research ideas in the field of ART in older women, in investigating factors that may improve outcomes. The limitations of this study are, data was collected from patient records which limits information details and increases the risk of missing data. It is also a retrospective analysis and that offers an inferior level of evidence in comparison to prospective studies or randomised controlled trials. Other confounding variables such as co morbidities that could affect female fertility hence affect the outcomes of ART were not addressed. The sample size was small & hence not representative of the population at large.

CHAPTER 5: CONCLUSIONS AND RECOMMENDATIONS

CONCLUSION:

Reproductive outcomes of ART of women 40 years & older are associated with a low success rate of 0,7% LBR and 3,3% CPR/OPR in this study. This study also reported high rates of miscarriage (66%). Oocyte aging and poor oocyte quality as illustrated by high cycle cancellation rates (31%), low number of oocytes collected during aspiration and poor embryo development seems to be the main reason for poor outcomes in this study. There were no cases of HOMP, which was reassuring. We do believe that infertility and contraception should be communicated under one platform in sexual and reproductive health and to raise public awareness about age-related fertility decline. This will allow women who wish to delay childbearing due to personal, health or social reasons to explore options such as egg freezing earlier in life rather than later.

FUTURE STUDY RECOMMENDATIONS:

The study findings stimulate debate around ART service provision for older women in limited resource settings. It also highlights the need for more studies that will be required to address issues related to the type of patient profile and other markers that could identify candidates with better chance and prognosis.

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APPENDICES

APPENDIX 1

UNIVERSITEIT STELLENBOSCH UNIVERSITY

Health Research Ethics Committee (HREC)

Approval Notice

New Application

23/01/2019

Project ID :1514

HREC Reference #: S17/09/185

Title: OUTCOMES OF ART IN OLDER WOMEN (40 YRS & OVER) AT TYGERBERG HOSPITAL

Dear Dr Nontando Nkangana,

The **Response to Stipulations** received on 21/01/2019 18:13 was reviewed by members of **Health Research Ethics Committee 2 (HREC2** via **expedited** review procedures on 23/01/2019 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Period: This project has approval for 12 months from the date of this letter.

Please remember to use your **Project ID [1514]** on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review

Please note you can submit your progress report through the online ethics application process, available at: Links Application Form Direct Link and the application should be submitted to the HREC before the year has expired. Please see *Forms and Instructions* on our HREC website (www.sun.ac.za/healthresearchethics) for guidance on how to submit a progress report.

The HREC will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Departement of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website https://applyethics.sun.ac.za/ProjectView/Index/1514

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Mr. Francis Masiye ,

HREC Coordinator,

Health Research Ethics Committee 2 (HREC2).

National Health Research Ethics Council (NHREC) Registration Number:

Page 1 of 2

REC-130408-012 (HREC1)·REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number: IRB0005240 (HREC1)·IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects; the South African Department of Health (2006). Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

APPENDIX 2

27 Nassau Street
Parrow
Cape Town 7505
19 December 2018

To: The Health Research Ethics Committee
University of Stellenbosch

RE:APPLICATION FOR CONSENT WAIVER

I, Dr N S Nkangana will be conducting a retrospective descriptive study on the outcomes of assisted reproductive technologies in older women (40yrs & above); and would therefore like to apply for waiver of consent.

The lab personnel, my supervisor & I will have access to the medical records. Data will be collected using hospital medical records that are locked in the reproductive medicine department laboratory. The research will pose no risk to the participants nor will it affect their rights & welfare. There will be minimal risk of invasion of patient's privacy as data will be collected using folder numbers, no identifiable information will be used & the data will be coded to protect the patients' identities.

I hope my request will receive your favourable consideration

Yours faithfully

N S Nkangana
Medical Registrar
Department of Obstetrics & Gynaecology

APPENDIX 3: EXCEL DATA COLLECTION TABLE

Number Year	Name Female	Name Male	LABNr	Date Procedure	DOB	Patient Age	Donor Age	Oocyte Age	Surr

CycleNR	PrimSecINF	FDiag	HydrosalPX	HYD Removed	Endo	AMH	BMI	HIV Status Fem	MDiag

Donor Sperm	HIV Status Male	PCOS	Semen Parameters				
			Count		Motility		Morphology (%)

Semen Coll	Semen Prep	Procedure	StimProt	NROocytes	NRImmature	NRMII	NrFert	DAY 2	DAY 3

GQE				PQE					
DAY 4	DAY5	DAY6	DAY7	DAY 2	DAY 3	DAY4	DAY5	DAY6	DAY7

Misc		FSac	FH	FreezeAll	Remarks
<7weeks	>7weeks				